STRIKING UP THE CONVERSATION: QUORUM SENSING IN FUNGI

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ABSTRACT

Quorum sensing is a form of communication observed in different species of microbes. Numerous studies have shown the ability of bacteria and fungi to carry out quorum sensing by releasing specific molecules to enable communication in a large population. Quorum sensing has been shown to influence growth, morphology, and other factors pertaining to virulence in pathogenic microbes. In this review, we address three important fungal species and explain how each fungus has a unique and dynamic way of communicating. *Candida albicans* is an opportunistic pathogen, or one that is part of the normal microbiota that can become pathogenic and cause several diseases. Here, we address two quorum sensing molecules (QSMs) identified by investigators. These chemicals are tyrosol and farnesol, which act together to control cellular growth, morphology and biofilm production. Another opportunistic fungal pathogen, *Cryptococcus neoformans*, has been shown to display quorum sensing activity by using pantothenic acid as well as a peptide called quorum sensing–like peptide 1. These molecules have both been shown to control growth rates of *C. neoformans*. *Saccharomyces cerevisiae* is another dimorphic fungus that uses QSMs, although it is nonpathogenic. Using two aromatic alcohols, phenylethanol and tryptophol, S. *cerevisiae* can alter pseudohyphal growth in diploid cells as well as invasive growth in haploid cells. By understanding more about the ways these organisms communicate, we present the potential for new and better targets for the treatment of fungal infections.

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INTRODUCTION

Many microbes use a form of communication known as quorum sensing, which is a function of population density. This phenomenon was first discovered in the bacteria *Vibrio fischeri* and *Vibrio harveyi* in the 1970s. These bacteria were shown to luminesce only when high numbers of bacteria cells were present (30, 31). In 2001, Hornby *et al.* reported evidence of a quorum sensing mechanism in the eukaryotic yeast *Candida albicans* (15). Similar to the process used by bacteria, fungal cell density was found to play a major role in communication (18, 25). Fungi, along with

other organisms, secrete compounds known as quorum sensing molecules (QSMs) into their environment to communicate with neighboring cells. QSMs, also known as autoinducers, regulate many functions of the population as a whole. QSMs must accumulate to reach high concentrations to have an effect on the organism. A large population of microbes, therefore, must be present to produce high enough levels of QSMs to have an effect (3). The QSMs bind receptors on the microbe's cell and when enough receptors are bound they activate signaling pathways. The induction of these signaling pathways affects gene expression in the organism, which in turn controls various cellular processes, including cell growth, biofilm formation, motility, cell morphology and secretion of virulence factors (1, 2, 8, 14, 25, 27, 45).

Much work has been done to uncover the various mechanisms that regulate quorum sensing by identifying the pathways and signaling proteins involved. For example, Kruppa *et al.* were the first to report a two-component signal transduction pathway in eukaryotic cells that mediates morphology, phenotype, and biofilm formation (18). Other recent studies have determined Ras1, cyclic AMP (cAMP), and mitogen-activated protein kinase (MAPK), among others, to be important factors for quorum sensing in both *C. albicans* and *Cryptococcus neoformans* (10, 20, 22).

Although more is known about quorum sensing in bacteria, this method of communication in fungal microbes has been an area of great interest in recent years. Quorum sensing in *Candida albicans* is perhaps the best understood example of quorum sensing in fungi (3, 7, 10, 15, 35, 41, 45). In addition, *Cryptococcus neoformans* and *Saccharomyces cerevisiae* have also been identified as fungal species that utilize this cellular communication (2, 6, 21, 22). This review will discuss the quorum sensing mechanisms that *C. albicans, C. neoformans,* and *S. cerevisiae* employ in regulating the cellular population, as these are the species in which fungal quorum sensing has been most thoroughly studied. Although other fungal species have been shown to have quorum sensing activities, the QSMs in these other species have not yet been identified. The significance of fungal quorum sensing will also be addressed as it applies to fungal signaling, the pathogenicity of fungi, and treatment of fungal infections.

CANDIDA ALBICANS

Candida albicans is a dimorphic fungus that has been extensively studied due to its unique ability to cause diseases even though it is part of the normal human microbiota. This fungus causes thrush, genital candidiasis, and bloodborne invasive candidiasis (16, 17, 20). An important attribute contributing to the virulence of *C. albicans* is its dimorphism, or the ability to switch morphological forms between mycelium (hyphae) and budding yeast. The mycelium form of fungi embeds into tissue, while the yeast form is associated with initiating infections and dissemination (32, 38). Two QSMs, farnesol and tyrosol, have been determined to have an effect on this dimorphism phenomenon as well as other cellular processes (7, 10, 15, 18, 20, 33).

Farnesol was discovered in 2001 and was the first QSM identified in a eukaryotic cell (Fig. 1) (15, 34). Farnesol, an isoprenoid, was identified as a QSM in *C. albicans* by observing the effects that supernatants from spent media (cell-free, filtered supernatant from a previously grown culture) had on the differentiation and mycelial growth of the fungi. The results of the assays showed that the highest amount of mycelial growth occurred when no supernatant was added.

Figure 1. Schematic diagram illustrating fungal quorum sensing molecules and their effects.

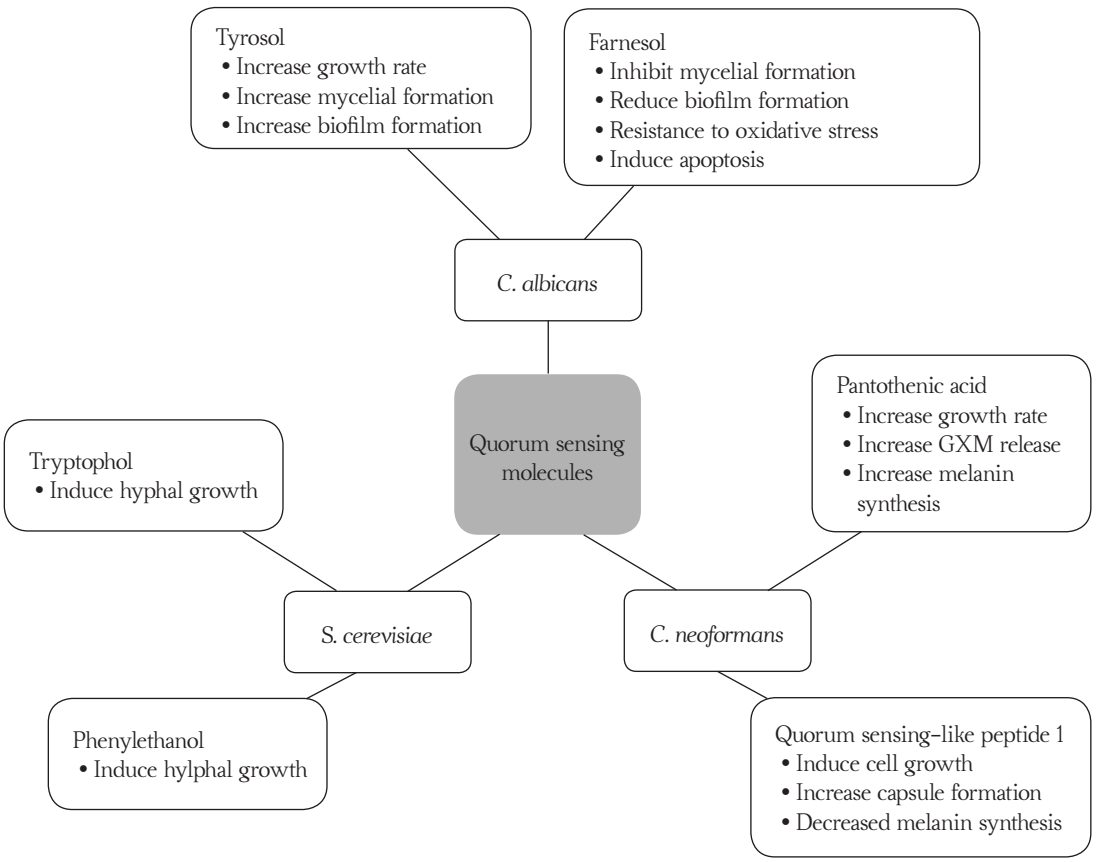


Table 1. Summary of quorum sensing in fungi

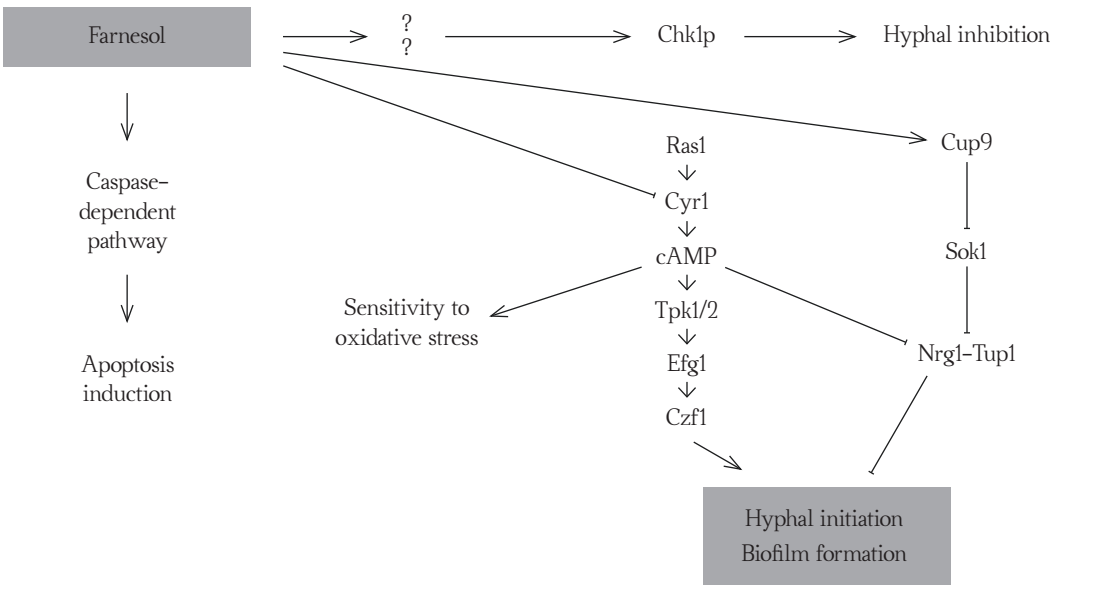
Organism	Quorum sensing molecule	Effect of quorum sensing molecule	References
Candida albicans	Farnesol	Prevent mycelial formation	15
		Reduce biofilm formation	35
		Increase resistance to oxidative stress	10,45
		Induce apoptosis	41
Candida albicans	Tyrosol	Increase growth rate	7
		Increase mycelial formation	7
		Increase biofilm formation	3
Cryptococcus neoformans	Pantothenic acid	Increase growth rate	2
		Increase GXM release	2
		Increase melanin synthesis	2
Cryptococcus neoformans	Quorum sensing-like peptide 1	Induce cell growth	21
		Increase capsule formation	22
		Decrease melanin synthesis	22
Saccharomyces cerevisiae	Phenylethanol	Induce hyphal growth	6
Saccharomyces cerevisiae	Tryptophol	Induce hyphal growth	6

When a high concentration of supernatant was added, the amount of mycelia was substantially decreased. This indicated QSMs had a dose-dependent effect on the morphology (15). To identify the QSM in the supernatant, solvent extraction of spent media was performed and coupled with thin-layer chromatography (TLC) and gas chromatography-mass spectroscopy (GC-MS). The use of these techniques combined with the elimination of other potential QSMs resulted in the identification of farnesol as the QSM responsible for the effect on mycelial growth of *C. albicans*. Commercially prepared farnesol also prevented mycelial formation; further suggesting that farnesol was the QSM responsible for the observed effect on morphology (Table 1). Growth rates were also observed when farnesol was added to *C. albicans* cultures and it was concluded that farnesol did not have an effect on yeast budding (15). The discovery of a molecule that inhibits mycelial formation is important because it is the mycelium form of the organism that allows it to enter the bloodstream, resulting in invasive candidiasis (15).

Researchers have demonstrated that farnesol inhibits the mycelial phase and promotes the yeast phase through the regulation of many different signaling pathways as depicted in Fig. 2. Chk1p was identified as a possible two-component signal transduction protein that acts with an unidentified upstream protein to mediate farnesol sensing. Authors tested a wild type strain and a Chk1 mutant strain of *C. albicans* and found that the Chk1 mutant germinated, resulting in mycelial growth, in the presence of farnesol while the others did not. This could be valuable knowledge because two-component signaling genes are not found in humans and could provide a potential therapeutic target for this fungal pathogen (18). In 2011, it was reported that farnesol suppresses hyphal formation through the inhibition of the Ras1-Cyr1-cAMP signaling pathway (10, 23, 34). In fact, cells with increased cAMP signaling are more resistant to the morphology effects of farnesol (23). Tpk1/2, Czf1, and Efg1 were discovered to be required for the morphology effects of farnesol. These findings are in line with the previous studies, as Tpk1/2, Efg1, and Czf1 are downstream of the Ras1-Cyr1-cAMP pathway (20). Farnesol signaling was discovered to lead to resistance to oxidative stress, also due to inhibition of the Ras1-Cyr1-cAMP pathway (10). The discovery of farnesol enabling the cell to resist oxidative stress provides an additional mechanism farnesol uses to aid in the pathogenicity of *C. albicans* (10, 45).

Evidence also suggests that the transcription regulator Tup1 plays a role in the inhibition of mycelial formation in response to farnesol. Although Tup1 seems to play a role in the effects of farnesol signaling, the signaling pathway linking Tup1 to farnesol-mediated morphology effects is still unclear (20). The involvement of Tup1 in quorum sensing of *C. albicans* is especially interesting because Tup1 is also involved in quorum sensing in *C. neoformans*, which will be discussed later in this review (20, 21). Furthermore, Nrg1 was discovered to have a crucial role in the farnesol-dependent inhibition of hyphal formation (25). Nrg1 inhibits hyphal formation and therefore must be absent for hyphal initiation. The absence of Nrg1 is controlled by two mechanisms: 1) The Ras1-Cyr1-cAMP pathway has a negative effect on *NRG1* transcription and 2) protein degradation of Nrg1. Farnesol inhibits the Ras1-Cyr1-cAMP pathway, resulting in the expression of *NRG1* which results in inhibition of hyphal formation. In addition, farnesol blocks Nrg1 degradation by stabilizing the Cup9 transcriptional repressor, which in turn represses *SOK1* expression.

Figure 2. A diagram depicting the pathways that have been implicated in farnesol signaling in *C. albicans*.



Sok1 leads to the degradation of Nrg1, therefore a repression of *SOK1* results in inhibition of Nrg1 degradation thus allowing Nrg1's presence to inhibit hyphal formation. Interestingly, both the Ras1-cAMP pathway and the Cup9-Sok1-Nrg1 pathway are required for farnesol to elicit its effects on the morphology of *C. albicans* (Fig. 2) (25).

Additional effects of farnesol on *C. albicans* include the induction of apoptosis *via* a caspase-dependent pathway (Table 1) (41). In addition, farnesol was shown to induce apoptosis and decrease proliferation in human oral squamous carcinoma cells (39). The ability of farnesol to affect cell death may have important implications for the development of therapies for fungal infections and for cancer (39, 41).

Tyrosol is another QSM produced by *C. albicans* that regulates growth and morphology (Table 1) (7). Tyrosol increases fungal growth by substantially decreasing the length of time the fungus is in lag phase. This was observed when Chen *et al.* (6) compared the growth of dilute overnight *C. albicans* cultures in the presence and absence of tyrosol over an 8-hour period. They also demonstrated that tyrosol is continuously released into the medium during growth and that it promotes filamentous morphology. Tyrosol was shown to promote germ tube formation, stimulating the conversion of yeast cells to hyphae (Fig. 1). The effect tyrosol has on cell growth may be due to tyrosol stabilizing transcripts that encode proteins involved in DNA synthesis and the cell cycle, therefore affecting growth by regulating the processes of DNA synthesis and the cell cycle (7). These results suggest that tyrosol and farnesol work together to control cellular growth and morphology of *C. albicans* (7).

Another important factor contributing to the virulence of some pathogens is biofilm

formation. Biofilms play an important role in natural and medical environments. Biofilms are organized microbial communities that adhere to surfaces, posing a serious health threat for patients with medical devices like stents and catheters (35). The mycelium form of fungi is crucial for biofilm development of *C. albicans*; therefore, inhibiting mycelial formation could be important for controlling fungal biofilms (35). Studies done by Ramage *et al.* and Kruppa *et al.* demonstrated that farnesol had a direct effect on biofilm formation (Table 1) (18, 35). The amount of biofilm formation was reduced as the concentration of farnesol increased. There was a 60% reduction in biofilm formation when the wild type strain of *C. albicans* was exposed to 25 μM and 250 μM of farnesol (18). Ramage *et al.* hypothesized that the reduction in biofilm formation was due to the fact that farnesol decreased mycelial formation, which is crucial for biofilm development of *C. albicans*. They concluded that this was a mechanism the organism uses to control overgrowth and limit competition (35). Microarray analysis comparing *C. albicans* biofilms inhibited by farnesol to natural *C. albicans* biofilms shows expression changes in genes controlling hyphal formation, drug resistance, cell wall maintenance and iron transport (4).

Interestingly, when tyrosol was added to *C. albicans* during different stages of biofilm formation, there was no effect observed. When farnesol and tyrosol were added together, the effect was dependent on the combination of the individual concentrations of the two QSMs. Tyrosol eliminated the inhibitory effect of low concentrations of farnesol. However, tyrosol was unable to overcome farnesol's inhibition of biofilm formation when 1 mM of farnesol was used. In addition, biofilms exposed to both farnesol and tyrosol were almost entirely in the yeast form suggesting that farnesol has a dominant effect. These discoveries could lead to farnesol as a possible treatment for fungal biofilms (3). As shown in Table 1, the QSMs produced by *C. albicans* affect multiple aspects of its pathogenicity, including: morphology, biofilm formation, and resistance to oxidative stress. These quorum sensing molecules require additional study to further investigate this common opportunistic fungus.

CRYPTOCOCCUS NEOFORMANS

Cryptococcus neoformans is another dimorphic fungal microbe and can cause life-threatening meningitis, particularly in AIDS patients (5, 19). Quorum sensing is not as well understood in *C. neoformans;* however, it appears to play a significant role in the regulation of several cellular processes of the fungus (Fig. 1). It was observed that when the gene for the transcriptional repressor *TUP1* is disrupted, *C. neoformans* colonies were less than 1% of the normal size and number compared to cells expressing *TUP1* (21). The authors also discovered that growth of *TUP1* mutants (*tup1*Δ) was dependent on the density of cells. This cell density dependent phenotype is an indication *C. neoformans* participates in quorum sensing. When a low cell number of *TUP1* mutants were plated, no growth occurred. Even though a growth or no-growth phenotype had not previously been described as an effect of quorum sensing, the effects of TUP1 on growth would seem to indicate quorum sensing is involved. The effect TUP1 has on the growth of *C. neoformans* was shown when *tup1*Δ strains were grown on conditioned medium (filtered supernatant from a previously grown culture) from cultured *tup1*Δ cells. At low cell numbers, the cells placed in conditioned medium formed colonies, while cells plated at the same low cell number,

but without conditioned medium failed to grow (21). The molecule in the conditioned medium responsible for this activity is quorum sensing–like peptide 1 (QSP1) (Table 1). The investigators artificially synthesized QSP1, placed it in media with *tup1*Δ strains and observed that growth patterns were just as strong as the *tup1*Δ strains grown in conditioned medium (21).

In addition to growth regulation, TUP1 has been determined to play a role in the pathobiology of *C. neoformans*. For example, Lee *et al.* demonstrated that TUP1 regulates iron and copper utilization, which are known modulators of melanin synthesis, a pigment produced by *C. neoformans* that contributes to its pathogenicity (22). Melanin plays a role in the protection of the yeast from oxidative stress (24). Melanin production is controlled by the laccase enzyme, which requires copper ions to function. Gene mutations resulting in a loss of metal ion homeostasis can therefore result in a lack of melanin production, which can be overcome by the addition of copper. Lee *et al.* observed a reduction in melanin synthesis in the *tup1*Δ strain that was restored after the addition of 10 μM $CUSO_4$ (22). This suggests TUP1 has an effect on metal ion homeostasis and therefore melanin synthesis.

Additional studies also showed melanization was cell density–dependent, indicating a quorum sensing effect. Melanin production began when the cell density reached 4 x 10^7 CFU/ml. It was observed that the rate of melanization increased as the cell density increased (11). The capsule, which plays a role in the pathogenicity of *C. neoformans*, was also shown to be regulated by TUP1. Lee *et al.* reported a significant increase in capsule size of the *tup1*Δ strain compared to the wild-type strain (22). The capsule, composed primarily of glucuronoxylomannan (GXM), protects the yeast from phagocytosis and aids in dissemination (24). Finally, the *tup1*Δ strain of *C. neoformans* was demonstrated to be less virulent than the wild-type strain. Mice were infected with both strains and observed. Mice inoculated with the wild-type lived for 9 days while those inoculated with *tup1*Δ lived for 20 days (22). Thus, the effect on virulence is a result of the multiple effects TUP1 has on *C. neoformans* (Fig. 1).

Albuquerque *et al.* described quorum sensing in *C. neoformans* after they observed regulation of fungal activity dependent on cell density (2). They determined quorum sensing was involved in the regulation and production of several cellular components of the yeast such as the capsule and melanin. Investigators took conditioned medium from *C. neoformans* cultures and placed it in fresh *C. neoformans* cultures. Conditioned medium caused increased growth rates, GXM release, and melanin synthesis. Pantothenic acid was identified as a key component of these observed quorum sensing effects (Table 1) (2). Pantothenic acid was identified by conducting mass spectrometry and NMR. When pantothenic acid was placed in cultures, the same quorum sensing effects seen with conditioned medium were observed. It was found that higher concentrations of synthetic pantothenic acid were required to reproduce the effect seen from the concentration of pantothenic acid naturally found in conditioned medium. The authors also found the effects caused by pantothenic acid alone were not to the same extent as conditioned medium, indicating that some other molecule plays a role in the quorum sensing activity. Pantothenic acid was found to be an important bioactive molecule that most likely works in concert with one or more other molecules to produce the quorum sensing effects (2). At this time, there is not a definitive identification of the

other QSM(s) that may be utilized by *C. neoformans*. Interestingly, the growth rate of *C. neoformans* was also increased, to a lesser extent, by conditioned medium produced by *Cryptococcus albidus*, *Candida albicans*, *Saccharomyces cerevisiae*, *Sporothrix schenckii*, and *Blastomyces dermatitidis* suggesting there may be QSMs produced by other fungi that have an effect on *C. neoformans* (2).

C. neoformans produces GXM and melanin, two important cellular components of the yeast that contribute to its pathogenicity. The QSMs addressed are capable of increasing GXM production as well as decreasing the time required for both GXM and melanin production. They have also been shown to control growth (Fig. 1) (2, 21). A virulence factor of *C. neoformans* that is known to be regulated by the environment is antiphagocytic protein 1 (App1) (46). One possible future study would be to test if quorum sensing has an effect on the expression of App1 or other factors of the yeast. *C. neoformans* appears to have a complex quorum sensing system, but more research is needed to identify all of the strategies this yeast uses to survive inside the host.

SACCHAROMYCES CEREVISIAE

Saccharomyces cerevisiae is a nonpathogenic, dimorphic fungus. Its morphology has been shown to be auto-controlled by QSMs. When *S. cerevisiae* cells were placed in conditioned medium produced from cultures in the stationary phase, the *FLO11* gene used for hyphal formation was upregulated five-fold (6). The two QSMs discovered to be causing this effect are two aromatic alcohols, phenylethanol and tryptophol (Table 1). During nitrogen starvation, phenylethanol and tryptophol induce pseudohyphal growth in diploid cells and invasive growth in haploid cells (Figure 1). Filamentous growth was observed even with low concentrations of each molecule; however, when the molecules were combined the effect on filamentation was even higher (6). Tpk2p, a component of the PKA signal transduction pathway, and Flo8p, a transcription factor, are required for the upregulation of *FLO11*. These findings indicate that *S. cerevisiae* uses the PKA pathway to control morphology.

In addition to nitrogen starvation, cell density also affects the release of QSMs. High density cultures produce more phenylethanol and tryptophol per cell than do low density cultures. In addition, this work discovered a link between quorum sensing and nutrient sensing (6). Although this yeast is non-pathogenic, it is important to learn more about how the organism communicates at a population level, to add to the body of knowledge of fungal quorum sensing.

SIGNIFICANCE AND CONCLUSION

Quorum sensing is a complex phenomenon that allows microorganisms to communicate and regulate many processes. Communication is accomplished through molecules, known as quorum sensing molecules, which are released into the extracellular environment. QSMs must accumulate to reach a concentration threshold in order to have an effect on the organism. These molecules bind to receptors on the organism's cells and once enough receptors are bound they activate signaling pathways. Many fungi utilize

quorum sensing to affect pathogenicity by controlling growth rates, morphology, gene expression, biofilm formation, and virulence factors, all at a population level. The understanding of these mechanisms is of great importance in today's world and needs extensive attention due to the prevalence of fungal infections and the need for new and better antifungal therapies. Table 1 gives a summary of the QSMs discussed in this review. In *C. albicans*, farnesol aids in altering the morphology of the fungi by inhibiting hyphal formation, while tyrosol promotes hyphal formation and increases growth rates (7, 15, 35). *C. neoformans* QSMs are not as well-known as those of other microbes. Pantothenic acid was identified as a QSM in *C. neoformans*; however, it appears other molecule(s) also play a role in the quorum sensing effects of this organism. Pantothenic acid was found to affect the growth rate, melanin production, and GXM release of *C. neoformans* (2). Peptides have been known for some time to have quorum sensing properties in bacteria; the peptide QSP1 is able to have quorum sensing-like effects on the growth of the fungal species *C. neoformans* (21). In *S. cerevisiae*, the QSMs that have been discovered are the aromatic alcohols phenylethanol and tryptophol. These molecules induce hyphal growth (6).

Quorum sensing was a significant discovery as many of the processes it affects are required for the pathogenicity of microbes. One of the most interesting hypothesized reasons bacteria use quorum sensing is to remain hidden from the host's immune system until a large population of the pathogen has grown. This allows the bacteria to grow in number and be ready to overcome the host's immune response before releasing virulence factors that activate the host's immune response (12). It has even been observed that host organisms have the ability to inhibit quorum sensing in bacteria by mimicking QSMs that the bacteria secrete. These host organisms include the macro alga *Delisea pulchra*, as well as several plant species (26, 43). Macroalgae and plants have been shown to inhibit the most well-known QSM, *N*-acyl-homoserine lactone (AHL), which is produced by many Gram negative bacterial species. The inhibitor molecules were found to compete with AHL molecules for their receptor, which is the LuxR receptor. By binding and blocking the receptor, the inhibitors prevent AHL-dependent signaling. This finding was further supported by findings that these inhibitor molecules also inhibit AHL-dependent processes in *V. fischeri*, *P. aeruginosa*, *V. harveyi*, and *E. carotovora*.

The discovery of these natural methods of inhibiting quorum sensing led to studies aimed at developing drugs that will inhibit quorum sensing (12). There are three potential mechanisms to inhibit quorum sensing systems: [a)] inhibit the production of the QSMs, [b)] degrade the QSMs, and [c)] block the QSM receptor (36). More recent studies have resulted in the identification of compounds that inhibit quorum sensing in pathogenic bacteria (9, 37, 42, 44). The use of quorum sensing inhibitors is of great interest as potential therapeutics to bacterial infections due to the increasing rate of resistance to conventional antibiotics.

In this review, we discussed the quorum sensing processes and QSMs in fungi. Knowledge of how fungi participate in quorum sensing has great potential for improved medical treatments and preventions. For example, farnesol produced by *C. albicans* shows potential as a preventative option against biofilm formation, which could be important, as biofilm formation on medical devices is an emerging problem in patient care (35). Farnesol was demonstrated to have protective effects in mice with oral candidiasis

(13). Another study showed farnesol to aid the effects of certain antifungal drugs against *C. albicans* and alter drug efflux (40). While these studies have shown farnesol to result in a less severe infection, other studies have shown farnesol increases virulence of *C. albicans*. One group discovered that farnesol given to mice with systemic candidiasis resulted in an increase in virulence (28). The effect farnesol had on the virulence of *C. albicans* was a result of modulation of the host's cytokine response (29). These contrasting studies on the effect of farnesol on pathogenicity demonstrate the complexity of the effect of QSMs on fungi and fungal infections. In particular, farnesol may have a different effect on the pathogenicity of localized *C. albicans* infections compared to systemic infections.

Due to the growing threat of fungal infections, new and better therapeutics are needed for these infections. The modulation of quorum sensing in fungi represents a promising potential mechanism of new antifungal therapies. This treatment approach is especially promising due to the ability to target fungal cells with the potential for little to no effect on mammalian cells. More research is needed to understand quorum sensing in fungi and uncover methods of regulating these processes.

Many current antifungal treatments are toxic and costly. Thus, exploration into quorum sensing may be very beneficial in this area (2). Quorum sensing in bacteria has become a growing area of research due to the increasing number of drug resistant bacteria. Inhibiting cell–to–cell communication could be beneficial by targeting one type of bacteria in a host's microbiota while not harming the whole population (12). This strategy could potentially be used to treat fungal infections as well, while potentially preventing the overwhelming side effects of the commonly used antifungals. Many QSMs overlap in different microbes. This may conceivably represent a form of competition that may be exploited to target pathogenic fungi. Insights gained from studies on fungal quorum sensing provide potential for the development of new therapeutics aimed at treating and preventing fungal infections.

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